Clinical trial results:
Metformin treatment vs a diabetes model of antenatal care in women with mild fasting hyperglycaemia diagnosed in pregnancy: a pilot study

Summary

EudraCT number	2013-004065-13
Trial protocol	GB
Global end of trial date	04 January 2017

Results information

Result version number	v1 (current)
This version publication date	02 May 2020
First version publication date	02 May 2020

Trial information

Trial identification

Sponsor protocol code	Metform02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Manchester University NHS Foundation Trust
Sponsor organisation address	Oxford Road, Manchester, United Kingdom, M13 9WL
Public contact	Dr Lynne Webster, Manchester University NHS Foundation Trust, +44 01612764125, research.sponsor@mft.nhs.uk
Scientific contact	Dr Lynne Webster, Manchester University NHS Foundation Trust, +44 01612764125, research.sponsor@mft.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2017
Global end of trial reached?	Yes
Global end of trial date	04 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study aims to assess the acceptability and feasibility of using a simple treatment with tablets (metformin) for women with mild gestational diabetes. Metformin is safe in pregnancy and has the advantage that frequent blood glucose monitoring is not necessary. We hope this treatment will be effective in reducing the number of babies which gain excessive weight in pregnancy, without the need for frequent hospital visits and high intervention rates which are associated with the intensive antenatal care routinely offered to women with gestational diabetes.

Protection of trial subjects:

Metformin is associated with a number of gastrointestinal side effects and women unable to tolerate the drug will be advised to discontinue (<5% from previous studies). Although metformin treatment aims to reduce blood glucose levels before and after eating, serious hypoglycaemia is very uncommon and metformin is prescribed in several settings without regular blood glucose monitoring. Women randomised to the diabetic antenatal care arm of the study will be asked to perform regular blood glucose monitoring (BGM). This is an onerous task for women in pregnancy but is standard practice within diabetic antenatal clinics. Women who have HBGM outside the target range will be prescribed metformin and those who do not meet target control with metformin will be prescribed adjuvant insulin. This prescribing regime will be in line with current prescribing practices within our hospital. Women in this arm of the study will also be offered monthly ultrasound scans to assess fetal growth. It is usual practice to offer induction of labour to women with a macrosomic fetus (>95th centile)and therefore some women in this group will be offered additional obstetric interventions. Metformin can sometimes cause some stomach upset (sickness and diarrhoea) so the dose will be increased slowly to minimise this side effect. Metformin can also cause taste disturbance and affect appetite. There is a very rare (<1/10,000), but serious side effect of metformin called 'lactic acidosis'. This occurs in individuals with kidney or liver problems. We will perform a blood test at the beginning of the study to ensure that you do not have any liver or kidney problems before you start the metformin tablets to ensure that the treatment is safe for you. Other very rare side effects include skin rashes.

Background therapy:

Standard diabetes antenatal care (NICE diabetes guidelines) with HBGM and scan surveillance.

Evidence for comparator:

The pregnancy outcomes for all women, delivered at St Mary's Hospital Manchester in 2010, who had an oral glucose tolerance test (OGTT) which would fit the proposed IADPSG diagnostic criteria, have recently been reviewed. 4% of all women who had an OGTT had isolated mild fasting hyperglycaemia (fasting 5.1-5.4 mmol/L; 2 hour <8.5mmol/L). All of these women were managed in normal antenatal clinics with no treatment. The frequency of large for gestational age babies (LGA) in this group (defined as >95th centile using centiles adjusted for maternal characteristics, fetal gender and gestation) was 16.4% (95% CI 9.0-27.8%), more than three times the expected frequency. In addition, we have analysed the Manchester data collected as part the HAPO study (n=2388). In this cohort, 201 women (8%) had a fasting blood glucose level between 5.1 and 5.4 mmol/L (normal 2 hour; <8.5mmol/L). The frequency of LGA (>95th centile) in this group was 9.0% compared to 3.9% (p=0.002) in the normoglycaemic group (n=1886) (OR 2.2 (95% CI 1.4-3.3). This data also suggests that the frequency of macrosomic infants delivered to women with mild degrees of fasting hyperglycaemia in the third trimester is unacceptably high. It is therefore timely to determine whether a simple intervention in this group could reduce the number of macrosomic infants delivered. This pilot study will assess the acceptability of metformin, prescribed in conjunction with routine antenatal care, compared to a standard diabetic model of antenatal care. In the study arm, metformin will be titrated up to the maximum tolerated dose in the absence of home blood glucose monitoring (HBGM). Women in the standard diabetic clinic arm will have their treatment titrated according to HBGM with the addition of insulin where blood glucose levels are out of target, this will allow us to make an assessment of the effectiveness of metformin in this group of women with mild fasting hyperglycaemia.

Actual start date of recruitment	02 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	40
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Over the course of this study we aim to recruit 60 women.

Pre-assignment

Screening details:

Women with risk factors for GDM (NICE 2008) will be offered an oral glucose tolerance test (OGTT) at 26 weeks gestation as part of their routine antenatal care. Women with mild GDM (Fasting 5.1mmol/l- 5.4 mmol/L; 2-hour <8.5 mmol/l) will be recruited into the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin

Arm description:

Women randomised to the study arm (Metformin only treatment arm) will be prescribed metformin tablets up to 2000mg from randomisation (26-28 weeks gestation) and will stop once they have delivered their baby.
Women will be asked to start with 500mg metformin (1 tablet, Once Daily) taken with food, increasing on Day 4 by an increment of 500mg per day (in other words to 1 tablet, twice daily). Day 7: a further increment of 500mg per day (in other words to 1 tablet, three times daily). On Day 14, women will increase the evening dose of metformin by a further 500mg. If side effects (largely anticipated to be gastro-intestinal) are experienced, the woman should drop to the previous dose or 500mg metformin (whichever is the greater) and wait for 3 days before increasing the dosage again. The maximum recommended dose is 2000mg daily, taken as three divided doses. The usual starting dose is one tablet 2 or 3 times daily given during or after meals.

Arm type	Experimental
Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Women randomised to the study arm (Metformin only treatment arm) will be prescribed metformin tablets up to 2000mg from randomisation (26-28 weeks gestation) and will stop once they have delivered their baby.
Women will be asked to start with 500mg metformin (1 tablet, Once Daily) taken with food, increasing on Day 4 by an increment of 500mg per day (in other words to 1 tablet, twice daily). Day 7: a further increment of 500mg per day (in other words to 1 tablet, three times daily). On Day 14, women will increase the evening dose of metformin by a further 500mg. If side effects (largely anticipated to be gastro-intestinal) are experienced, the woman should drop to the previous dose or 500mg metformin (whichever is the greater) and wait for 3 days before increasing the dosage again. The maximum recommended dose is 2000mg daily, taken as three divided doses. The usual starting dose is one tablet 2 or 3 times daily given during or after meals.

Arm title	Standard care

Arm description:

In addition to dietary advice and lifestyle advice, women in the standard care arm will be issued with a HBGM meter and asked to record capillary blood glucose before and 1 hour after meals (x 7/day) with target glucose ranges of fasting <5.5 and 1 hour post prandial <7.8mmol/L. Women will be provided

with a contact telephone number and asked to contact the research midwife if the blood sugars are outside the target range on 3 or more occasions within one week. The handheld maternity records will be updated to inform health care professionals that the woman is participating in the trial and has been randomised to the standard care arm. A baseline ultrasound to assess fetal growth will be performed at study visit 1. Women will be reviewed in the research clinic 2 weeks after their initial appointment.

Arm type	model of care
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Metformin	Standard care
Started	20	20
Completed	17	19
Not completed	3	1
Physician decision	2	-
Transferred care	1	-
Discontinued intervention	-	1

Baseline characteristics

Reporting groups

Reporting group title	Metformin

Reporting group description:

Women randomised to the study arm (Metformin only treatment arm) will be prescribed metformin tablets up to 2000mg from randomisation (26-28 weeks gestation) and will stop once they have delivered their baby.
Women will be asked to start with 500mg metformin (1 tablet, Once Daily) taken with food, increasing on Day 4 by an increment of 500mg per day (in other words to 1 tablet, twice daily). Day 7: a further increment of 500mg per day (in other words to 1 tablet, three times daily). On Day 14, women will increase the evening dose of metformin by a further 500mg. If side effects (largely anticipated to be gastro-intestinal) are experienced, the woman should drop to the previous dose or 500mg metformin (whichever is the greater) and wait for 3 days before increasing the dosage again. The maximum recommended dose is 2000mg daily, taken as three divided doses. The usual starting dose is one tablet 2 or 3 times daily given during or after meals.

Reporting group title	Standard care

Reporting group description:

In addition to dietary advice and lifestyle advice, women in the standard care arm will be issued with a HBGM meter and asked to record capillary blood glucose before and 1 hour after meals (x 7/day) with target glucose ranges of fasting <5.5 and 1 hour post prandial <7.8mmol/L. Women will be provided with a contact telephone number and asked to contact the research midwife if the blood sugars are outside the target range on 3 or more occasions within one week. The handheld maternity records will be updated to inform health care professionals that the woman is participating in the trial and has been randomised to the standard care arm. A baseline ultrasound to assess fetal growth will be performed at study visit 1. Women will be reviewed in the research clinic 2 weeks after their initial appointment.

Reporting group values	Metformin	Standard care	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
Adults (18-64 years)	20	20	40
Age continuous Units: years			
median	31	33	
inter-quartile range (Q1-Q3)	26 to 34	28 to 35	-
Gender categorical Units: Subjects			
Female	20	20	40
Male	0	0	0
Smokers Units: Subjects			
Yes	1	0	1
No	19	20	39
Ethnicity Units: Subjects			
White	7	4	11
Black	4	5	9
Asian	6	7	13
Other	3	4	7

BMI			
Units: ratio			
median	31	29	
inter-quartile range (Q1-Q3)	27.5 to 35.0	25.5 to 34.0	-
Parity			
Units: Count			
median	1	1	
inter-quartile range (Q1-Q3)	0 to 2	0 to 2	-
Fasting gllucose at OGTT			
Units: mmol/L			
median	5.2	5.2	
inter-quartile range (Q1-Q3)	5.10 to 5.30	5.15 to 5.35	-
2H glucose at OGTT			
Units: mmol/L			
median	6.50	5.95	
inter-quartile range (Q1-Q3)	5.55 to 7.05	4.70 to 6.90	-
HbA1c at baseline			
Units: mmol/L			
median	33.5	32.0	
inter-quartile range (Q1-Q3)	30.0 to 35.0	29.0 to 37.0	-

End points

End points reporting groups

Reporting group title	Metformin

Reporting group description:

Women randomised to the study arm (Metformin only treatment arm) will be prescribed metformin tablets up to 2000mg from randomisation (26-28 weeks gestation) and will stop once they have delivered their baby.
Women will be asked to start with 500mg metformin (1 tablet, Once Daily) taken with food, increasing on Day 4 by an increment of 500mg per day (in other words to 1 tablet, twice daily). Day 7: a further increment of 500mg per day (in other words to 1 tablet, three times daily). On Day 14, women will increase the evening dose of metformin by a further 500mg. If side effects (largely anticipated to be gastro-intestinal) are experienced, the woman should drop to the previous dose or 500mg metformin (whichever is the greater) and wait for 3 days before increasing the dosage again. The maximum recommended dose is 2000mg daily, taken as three divided doses. The usual starting dose is one tablet 2 or 3 times daily given during or after meals.

Reporting group title	Standard care

Reporting group description:

In addition to dietary advice and lifestyle advice, women in the standard care arm will be issued with a HBGM meter and asked to record capillary blood glucose before and 1 hour after meals (x 7/day) with target glucose ranges of fasting <5.5 and 1 hour post prandial <7.8mmol/L. Women will be provided with a contact telephone number and asked to contact the research midwife if the blood sugars are outside the target range on 3 or more occasions within one week. The handheld maternity records will be updated to inform health care professionals that the woman is participating in the trial and has been randomised to the standard care arm. A baseline ultrasound to assess fetal growth will be performed at study visit 1. Women will be reviewed in the research clinic 2 weeks after their initial appointment.

Primary: Study compliance

End point title	Study compliance[1]

End point description:

End point type	Primary

End point timeframe:

Over study duration

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Subjects	17	19		

Statistical analyses

No statistical analyses for this end point

Primary: Intervention compliance with 2g

End point title	Intervention compliance with 2g[2][3]

End point description:

End point type	Primary

End point timeframe:

Overall

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.
[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a treatment specific endpoint designed to inform the future study around treatment adherence. Therefore it is not relevant to the control group and there is no equivalent measure.

End point values	Metformin			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Percentage				
median (inter-quartile range (Q1-Q3))	68 (48 to 85)			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum metformin dose

End point title	Maximum metformin dose[4][5]

End point description:

End point type	Primary

End point timeframe:

Whole study

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.
[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a treatment specific endpoint designed to inform the future study around treatment adherence. Therefore it is not relevant to the control group and there is no equivalent measure.

End point values	Metformin			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: mg				
median (inter-quartile range (Q1-Q3))	2000 (1000 to 2000)			

Statistical analyses

No statistical analyses for this end point

Primary: Happy to participate

End point title	Happy to participate[6]

End point description:

End point type	Primary

End point timeframe:

Completion

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Subjects				
Yes	18	17		
No	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: When you started the study, how did you feel about your allocation?

End point title	When you started the study, how did you feel about your allocation?[7]

End point description:

End point type	Primary

End point timeframe:

Duration

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: Subjects				
Not satisfied	0	0		
Satisfied	15	14		
Not sure	3	2		
Missing	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Now you have completed the study, how do you feel about your allocation?

End point title	Now you have completed the study, how do you feel about your allocation?[8]

End point description:

End point type	Primary

End point timeframe:

End of study

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: Subjects				
Not satisfied	0	0		
Satisfied	18	17		
Not sure	0	0		
Missing	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: How do you feel about your antenatal care since you enrolled in the study?

End point title	How do you feel about your antenatal care since you enrolled in the study?[9]

End point description:

End point type	Primary

End point timeframe:

Duration

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: subjects				
Not satisfied	0	0		
Satisfied	18	17		
Not sure	0	0		
Missing	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: If the study included a 'no treatment' allocation, would you have still been happy to take part in the study?

End point title	If the study included a 'no treatment' allocation, would you have still been happy to take part in the study?[10]

End point description:

End point type	Primary

End point timeframe:

Duration

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: Subjects				
Yes	14	16		
No	4	1		
Missing	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: How often did you forget to take your medication?

End point title	How often did you forget to take your medication?[11]

End point description:

End point type	Primary

End point timeframe:

Duration

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: Subjects				
No medication	0	4		
Never or rarely	12	8		
1-3 times/wk	5	5		
4-6 times/wk	0	0		
>6 times/wk	1	0		
Missing	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Which part of your diabetes treatment was easiest?

End point title	Which part of your diabetes treatment was easiest?[12]

End point description:

End point type	Primary

End point timeframe:

Duration

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: Subjects				
Doing finger-prick tests	0	7		
Being careful with diet	1	2		
Taking medication	16	7		
Missing	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: Which part of your diabetes treatment was hardest?

End point title	Which part of your diabetes treatment was hardest?[13]

End point description:

End point type	Primary

End point timeframe:

Duration

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: Subjects				
Doing finger-prick tests	0	7		
Being careful with diet	12	9		
Taking medication	4	0		
Missing	2	1		

Statistical analyses

No statistical analyses for this end point

Primary: In future pregnancy, if you developed diabetes again, would you choose?

End point title	In future pregnancy, if you developed diabetes again, would you choose?[14]

End point description:

End point type	Primary

End point timeframe:

Duration

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: Subjects				
Monitoring in a diabetic antenatal clinic	8	15		
Metformin, no home blood glucose / hospital visits	9	0		
No treatment at all	1	1		
Missing	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: HbA1C at 36-38 weeks

End point title	HbA1C at 36-38 weeks

End point description:

End point type	Secondary

End point timeframe:

36-38 weeks

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: mmol/L				
median (inter-quartile range (Q1-Q3))	35.5 (31.0 to 40.0)	37.0 (35.0 to 41.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of "none diabetes" scans

End point title	Number of "none diabetes" scans

End point description:

End point type	Secondary

End point timeframe:

Secondary

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Range				
median (inter-quartile range (Q1-Q3))	3 (2 to 5)	5 (0 to 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of clinic attendances post randomisation

End point title	Number of clinic attendances post randomisation

End point description:

End point type	Secondary

End point timeframe:

Duration

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Range				
median (inter-quartile range (Q1-Q3))	2.5 (2 to 5)	7 (4 to 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of phone calls

End point title	Number of phone calls

End point description:

End point type	Secondary

End point timeframe:

Duration

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Number				
median (inter-quartile range (Q1-Q3))	2 (1 to 4)	2 (0 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of admissions

End point title	Number of admissions

End point description:

End point type	Secondary

End point timeframe:

Duration

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Admissions	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Spontaneous labour onset

End point title	Spontaneous labour onset

End point description:

End point type	Secondary

End point timeframe:

Labour

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: Subjects	5	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Delivery - vaginal

End point title	Delivery - vaginal

End point description:

End point type	Secondary

End point timeframe:

Labour

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: Subjects	11	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Gestation at delivery

End point title	Gestation at delivery

End point description:

End point type	Secondary

End point timeframe:

Delivery

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: Days				
median (inter-quartile range (Q1-Q3))	278 (270 to 282)	273 (270 to 276)		

Statistical analyses

No statistical analyses for this end point

Secondary: LGA (greater than or equal to 95th centile)

End point title	LGA (greater than or equal to 95th centile)

End point description:

End point type	Secondary

End point timeframe:

Birth

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: Babies	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: LGA (greater than or equal to 4000g)

End point title	LGA (greater than or equal to 4000g)

End point description:

End point type	Secondary

End point timeframe:

Birth

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: Babies	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Centile

End point title	Centile

End point description:

End point type	Secondary

End point timeframe:

Birth

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: centile				
median (inter-quartile range (Q1-Q3))	45.5 (11.7 to 62.1)	33.95 (11.8 to 48.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: NICU admission

End point title	NICU admission

End point description:

End point type	Secondary

End point timeframe:
After birth

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: Babies	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Shoulder dystocia

End point title	Shoulder dystocia

End point description:

End point type	Secondary

End point timeframe:
After birth

End point values	Metformin	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: Babies	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The occurrence of adverse events will be sought by non-directive questioning of the patient during the study. Adverse events also may be detected when they are volunteered by the patient.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1

Reporting groups

Reporting group title	Metformin

Reporting group description:

Women randomised to the study arm (Metformin only treatment arm) will be prescribed metformin tablets up to 2000mg from randomisation (26-28 weeks gestation) and will stop once they have delivered their baby.
Women will be asked to start with 500mg metformin (1 tablet, Once Daily) taken with food, increasing on Day 4 by an increment of 500mg per day (in other words to 1 tablet, twice daily). Day 7: a further increment of 500mg per day (in other words to 1 tablet, three times daily). On Day 14, women will increase the evening dose of metformin by a further 500mg. If side effects (largely anticipated to be gastro-intestinal) are experienced, the woman should drop to the previous dose or 500mg metformin (whichever is the greater) and wait for 3 days before increasing the dosage again. The maximum recommended dose is 2000mg daily, taken as three divided doses. The usual starting dose is one tablet 2 or 3 times daily given during or after meals.

Reporting group title	Standard care

Reporting group description:

In addition to dietary advice and lifestyle advice, women in the standard care arm will be issued with a HBGM meter and asked to record capillary blood glucose before and 1 hour after meals (x 7/day) with target glucose ranges of fasting <5.5 and 1 hour post prandial <7.8mmol/L. Women will be provided with a contact telephone number and asked to contact the research midwife if the blood sugars are outside the target range on 3 or more occasions within one week. The handheld maternity records will be updated to inform health care professionals that the woman is participating in the trial and has been randomised to the standard care arm. A baseline ultrasound to assess fetal growth will be performed at study visit 1. Women will be reviewed in the research clinic 2 weeks after their initial appointment.

Serious adverse events	Metformin	Standard care	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Shoulder dystocia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Metformin	Standard care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)	1 / 20 (5.00%)	
Pregnancy, puerperium and perinatal conditions			
Baby not moving			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Reduced fetal movements			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Generally unwell			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Vomitting			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal cramps			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Breathless			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2014	SA01 - TBC - need summary of changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None.

Notes: